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The impact of statin therapy on the survival of patients with gastrointestinal cancer

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ABSTRACT

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that may play an important role in the evolution of cancers, due to their effects on cancer cell metabolism. Statins effect several potential pathways, including: cell proliferation, angiogenesis, apoptosis and metastasis. The number of trials assessing the putative clinical benefits of statins in cancer is increasing. Currently, there are several trials listed on the global trial identifier website clinicaltrials.gov. Given the compelling evidence from these trials in a variety of clinical settings, there have been calls for a clinical trial of statins in the adjuvant gastrointestinal cancer setting. However, randomized controlled trials on specific cancer types in relation to statin use, as well as studies on populations without a clinical indication for using statins, have elucidated some potential underlying biological mechanisms, and the investigation of different statins is probably warranted. It would be useful for these trials to incorporate the assessment of tumour biomarkers predictive of statin response in their design. This review summarizes the recent preclinical and clinical studies that assess the application of statins in the treatment of gastrointestinal cancers with particular emphasize on their association with cancer risk.

Key words: Statins, survival of patients, gastrointestinal cancer

Introduction

Gastrointestinal (GI) cancer is the third most common cause of cancer death globally, with more than 700,000 deaths a year[1]. Gastrointestinal cancers include: esophageal, stomach, liver, pancreas, and colorectal cancer (CRC)[2, 3]. Patient with late stage GI cancer have a poorer survival and drug efficacy[4]. Gastrointestinal cancers may be the consequence of non-regulation of many cellular and molecular activities such as apoptosis, cell cycle, proliferation, and DNA repair [5-7]. The pathways, and molecules involved in the development of cancer, require different treatments. Several cohort studies have demonstrated that increased cholesterol intake plays an important role in cancers such as colorectal cancers.[8, 9] Several studies have shown that, statins may reduce the incidence of several gastrointestinal cancers[10-13]. Kuoppala, J., et al. (2008) in a meta-analysis and systematic review on 42 trials (17 randomized controlled trials, 10 cohort studies, and 15 case-control studies) showed that, statins protect from stomach and liver cancers[14]. Singh and Singh demonstrated that, statin treatment was associated with a 32% reduction in the risk of GC[15].

Statins are inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase[16-18]. Statins were initially discovered in the 1970s and were approved to treat of hypercholesterolemia[19, 20]. This enzyme plays an important role in the mevalonate pathway and ultimately in the synthesis of cholesterol, reducing LDL-cholesterol [21, 22], and reducing cardiovascular disease morbidity and mortality.

Statins are actively transported into the cell via plasma membrane ATP-binding cassette (ABC) and solute carriers (SLC) superfamilies [23]. The ABC family of transporters consists of three members: P-glycoprotein (Pg-P/ ABCB1), breast cancer resistance protein (BCRP/ABCG2), and

multidrug resistance-associated proteins (MRP1/ ABCC1 and MRP2/ABCC2). A reduction in the activity of these proteins makes the statin more effective. [24]. The SLC superfamily is the family of organic anion transporting polypeptides (OATP/SLCO). Pharmacokinetics and pharmacodynamics of statins are dependent on changes in the SLC family[25].

As studies show, useful information may be obtained empirically or theoretically in the developments of drugs. On the other hand, discovering or designing drugs in health is very important, so many techniques are used. In this regard, the Nuclear Magnetic Resonance (NMR) has the unique ability to combine atomic spatial resolution with high temporal resolution in several widely different frequency regimes. This technique also gives us a lot of useful information about drugs, through 3D (three-dimensional) membrane protein structures[26-31]. As a hightropout technique, NMR provides a lot of information on chemistry, medicine or geophysics[32]. Thus this technique is the most beneficial techniques for drug discovery[27, 29]. To develop various prediction methods for proteome/genome analysis[33-39], the Chou's 5-step rules [40] should be followed. To timely get 3D structures of the target proteins the structural bioinformatics is needed[41-45].

Statins also play an important role in controlling Rho-A activity [46] in some disease such as cancers and HIV [47, 48] Kwak, B., et al. in 2000 demonstrated that, statins act as immunomodulatory via controlling MHC-II and T- lymphocyte activity[49]. Blocking MHC-II Statins decrease MMP-9 (matrix metalloproteinase 9)[50], downregulate B cell and T cell chemokine receptors, and improve Th1/Th2 cytokine balance. As well as, statins inhibit IFN β -1b[51].

On the other side, one of the goals of the pharmaceutical industry is the development of multi-purpose drugs that require a multi-label technique and approach[52-59]. Lee et al. showed that

simvastatin may improve the anti-angiogenic effects of bevacizumab in CRC through repressing angiopoietin2, BiP, and Hsp90 α in cancer cells[60]. As because of drug-drug interactions (DDI) between statins and antibiotics, doctors can avoid ordering clarithromycin and erythromycin for older patients who take cholesterol-lowering statin drugs[61]. To treat cancers and other diseases, knowledge of various posttranslational modification (PTM) positions in proteins, DNA, and RNA play a major role[62-64]. And the PseAAC [65, 66] and PseKNC[67-69] approaches are very useful in this.

Hence, a lot of studies developed to demonstrate the statin efficacy on disease such as cancers. In this regard, Klawitter, J., et al. in 2010, to demonstrate several target of antitumor activity of lovastatin, used a combination of proteomics and metabolomics[70]. Several studies have shown that, statins may also prevent cancers (Table 1) and reduce cancer mortality[71-73]. Brown and Goldstein showed that, mevalonate and cholesterol synthesis have an effect on cell growth[74]. Reducing mevalonate can effect cellular signaling, and cell cycle progression. [75] Statins also induce apoptosis via cell cycle arrest in G1 phase. This could have beneficial effects by inhibiting tumor development [76] in cancers including colorectal cancer(CRC). [77, 78]

CRC is a common GI cancer that is associated with a high mortality. Notarnicola et al. demonstrated that, the effects of HMG-CoA reductase in colorectal cancer cells is greater in relation to normal mucosal cells. It proposed that the cholesterol synthesis plays an important role in the development and evolution of CRC and may be potentially involved in the development of malignancy. [79] A meta-analysis of 32 trials by Bardou, et al. demonstrated that, statin treatment was associated with a reduction in CRC invasion and metastasis. Statins also appear to increase tumor sensitivity in combination with anti-cancer agents.[80] Gray et al. have shown that, the

likelihood of the survival in patients with CRC treated with statins is also increased.[81] There is a significant negative association between the use of long-term statin therapy and the risk of colorectal cancer[80, 82].

Virchow made a connection between cancer and inflammation[83]. The anti-inflammatory activity of statins has been reported in several studies [84]. They regulate important proinflammatory cytokine and molecule such as TNF, IL-6, IL-1[85, 86], CRP[87], CD 40 and CD40 L[88]. The activity of immune cells can be controlled by statins. MHC-II (major histocompatibility complexes class II) is controlled by statin via IFN- γ (interferon- γ) inhibition[89]. They down-regulate the expression of MHC-II that leads to a reduction in the differentiation and activation of Th1 and 2 (T helper 1)[89].

To alleviate the biased consequence caused by the imbalanced benchmark datasets in biomedical or biological systems[90-92], the IHTS (inserting hypothetical training samples) treatment[93, 94] is a very effective approach. To follow the role of statins within GI cancers trials, we summarize this review, which carries 29 clinical trials that include esophageal, stomach, pancreatic, gastric, liver, and CRC cancers.

The statin mechanisms involved in reducing CRC risk :

HMG-CoA reductase (HMGR) plays an important role in the mevalonate synthesis pathway. This enzyme produces mevalonic acid, a cholesterol precursor from HMG-CoA.[95] This process occurs predominantly in the liver, but occurs in all cells.[96] Statins may either be active (Atorvastatin, Cerivastatin, Fluvastatin and pravastatin), or pro-drugs (Lovastatin and Simvastatin). [97] Lovastatin, Simvastatin, Atorvastatin and Cerivastatin are metabolized by cytochrome P450 (CYP 3A4) and Fluvastatin via the CYP 2C9 pathway.[98, 99] Given the efficacy and safety of statins, they

are widely used to treat patients with hypercholesterolemia. Statins also have other pleiotropic effects, stimulating the development of new blood vessels[100], osteogenic stimulation[101], reducing serum C-reactive protein levels (CRP) [102].

Statin and cancers:

It has been reported that the statins probably act as a tumor suppressor in several different solid tumors, that include: esophageal[103], gastric[104], pancreatic[11], and rectal carcinoma[105]. In addition, statins may have beneficial effects on CRC in both prevention and treatment via several mechanisms[80]. Statins down-regulate the anti-apoptotic (BCL2 or cIAP1) and increase of proapoptotic (BMP) proteins that lead to apoptosis in CRC[106-109]. In addition statins cause the upregulation of other proapoptotic proteins such as bax and Bim[78, 110, 111]. It causes the release of cytochrome c from the mitochondria[112]. This process leads to enhanced caspase 9, as well as caspase 1,3, 7, and 8 directly[113, 114].

Statins may reduce cell proliferation[115], by G0/G1 cell cycle arrest[116] in CRC but also in breast cancer[117]. It may inhibit vascular endothelial growth factor (VEGF) as a major regulator of angiogenesis. Simvastatin inhibits VEGF via NF-KB, which is an angiogenic mediator. Thus statins inhibit proangiogenic pathways[107]. Studies have shown that the reduction in metastatic is rare by statins[118, 119]. however, Kusama et al. in a study on human pancreatic cancer cell invasion in vitro and experimental liver metastasis in vivo showed that, HMGR inhibitors may be potentially useful for clinical applications because of their anti-metastatic effects[120].

Statins can have beneficial effects on cancers via their epigenetic effects. Zeste homolog 2 (EZH2) acts as a silencer in epigenetic. statin increased p27^{KIP1} via EZH2, and finally statins inhibit

tumor progression[121]. Kodach et al. (2007) demonstrated that, SMAD4 plays an important role in the statin effect[122] .

Statins play an inhibitory role in cell cycle progression (Table 1). Tumor proliferation has been blocked by statins through cell cycle arrest via $P_{21}^{Cip1/WAF1}$ and P_{27}^{Kip1} expression. These molecules as cyclin dependent kinase (CDK) inhibitor, have been enhanced by statin and modulate cell cycle. That is why the cell cycle stopped at G1 stage[123, 124]. And also because, cyclin and CDKs play key a role in the cell cycle, statins via inhibition these causes arrest cell cycle[125]. Statins trough down-regulation of cyclin D1 (CycD), cyclin E (CycE), cyclin dependent kinase (CDK) 4 expression, and CDK2 prevent cancer cell growth. Inhibition of the phosphorylation of Retinoblastoma protein (Rb) is another putative mechanism, that allows statins to blocked the cell cycle. This occurs via stabilization of the transcriptionally passive complex E2F-Rb[126]. Farnesylated and geranylgeranylated proteins are reduced by HMGR inhibitors such as statins. These proteins make K-Ras and RHO/RAC respectively that are localized on plasma membrane[127]. This delocalization finally inactivated Rho-kinase pathway and is due to enhance cell migration, metastatic[128]. Tumors increase the anthracyclines sensitivity by inhibiting K-Ras farnesylation inhibition[129]. In addition, Akt and MAPK/ERK activity are inhibited by statins directly[130]. In the end, statins inhibit adapter protein 1 (AP1) and NF- κ B transcription factors[131].

Statins and CRC

Simvastatin induces apoptosis in models of colorectal cancer (HCT116) by stimulating the p38MAPK-p53-survivin cascade[132]. In xenograft models, simvastatin arrested angiogenesis[107]. One of the major causes of cancers are gene mutations. These may have a role in determining treatment. A K-Ras mutation is found in nearly 30% of patients with solid tumors. Statins can lower the expression of

the mutated KRAS protein by inhibition of protein prenylation. Therefore, this event make the Epidermal Growth Factor Receptor (EGFR) antibody susceptible to KRAS mutation in the CRC.[133] Simvastatin, when used with cetuximab, increases the anti-cancer function in KRAS mutation in human CRC cell line.[134] However in the NCT01190462 trials, 80mg simvastatin per day did not affect cetuximab susceptibility on KRAS gene mutation in the CRC patients. (NCT01190462) In the other study, a combination of 80mg simvastatin plus cetuximab and irinotecan was performed in the KRAS mutation of CRC by Lee, J., et al. This study showed that, compared to wild-type CRCs, no change in resistance to cetuximab was observed in KRAS mutation, and thus simvastatin may overcome cetuximab resistance(NCT01281761).[135] Some other clinical trials as combination anti-cancer therapy with simvastatin are registered. Panitumumab is another human monoclonal antibody directed against EGFR and was combined with simvastatin in the NCT01110785 trial. XELIRI (irinotecan plus capecitabine) and FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin) are other drugs that combined with simvastatin(NCT01238094). In this phase III randomised, placebo-controlled study, toxicity of the XELIRI or FOLFIRI didn't rise by simvastatin in low dose. 40 mg of simvastatin in this trial has no beneficial anti-cancer effects when combined with cytotoxic chemotherapy[136]. Another combination therapy of simvastatin with capecitabine, oxaliplatin, and bevacizumab for stage IV CRC is ongoing in phase II(NCT02026583).

FOLFIRI is combined with atorvastatin in step 1 in advanced colon or rectum adenocarcinoma in the NCT01605344 trial (Table 1).

Phase 3 trial of rosuvastatin for stage 1 and 2 colon cancer was undertaken in the NCT01011478 trial. Chemo radiation therapy (CRT) as the standard treatment of locally advanced rectal cancer plus rosuvastatin used in NCT02569645 trial. This phase 2 trial is for both prognostic and predictive of

response and toxicity to treatment that recognized genetic, serological, and pathological biomarkers (Table 1).

Statins and liver cancer

In cirrhosis, simvastatin has been tested in phase II trials to study Alpha-fetoprotein-L 3% (AFP-L3%) changes. (NCT02968810) Atorvastatin is used in the NCT03024684 trial to prevent the recurrence of hepatocellular carcinoma (HCC) after curative treatment, as well as pravastatin on HCC recurrence in early stage HCC patients at the trial of NCT03219372. The survivability, tumor responses, and PFS are the goals of the NCT03275376 study. In this study atorvastatin was used in HCC patients receiving sorafenib. Pravastatin is also included in NCT01903694 trial with sorafenib to measure their effect on overall survival in patients with HCC. The other study of pravastatin with sorafenib in patients with HCC is NCT01357486.

Statins in Gastric cancer

Because of progression-free survival (PFS) in advanced gastric adenocarcinoma was not improved by treatment with simvastatin plus capecitabine–cisplatin (XP) compare with XP alone, thus the NCT01099085 trial doesn't recommended low dose of simvastatin (40 mg) to chemotherapy in untargeted population with advanced gastric cancer (AGC)[137]. Statins have beneficial effects on inflammation through in a variety of ways, including reducing the synthesis of inflammatory cytokines[137]. The purpose of NCT01813994 trial was to evaluate the role of statin in gastric cancer by using inflammatory stomach variables on patients at high risk of gastric cancers.

Statins and pancreatic cancer

Simvastatin has side effect on pancreatic cancer by sonic hedgehog pathway deactivation. These beneficial effects can prevent live ability of tumor, tumor growth and metastasis. All this makes the gemcitabine more effective in pancreatic cancer [43]. The purpose of the NCT02201381 trial was to find the effect of metabolic therapy such as metformin, atorvastatin, doxycycline, and mebendazole in cancer patients.

Statins on esophageal Cancer

Pravastatin has been tested in NCT01038154 as a strong statin in advanced stage gastroesophageal cancer. The goal of the 4th phase of this study was to investigate the effect of pravastatin on survival and recurrence of advanced gastroesophageal cancer (NCT01038154).

Conclusion

There is growing body of data showing the therapeutic potential value of statins in the treatment of GI and their roles in carcinogenesis, due to their effect on the cancer cell metabolism. They can modulate several cellular and molecular processes including cell proliferation, metastasis, angiogenesis, and apoptosis, via inhibiting the downstream production of isoprenoids, matrix metalloproteinases, Ras/Rho, RAF/MEK-ERK pathways as well as cyclin-dependent kinases. It has also reported to be involved in the degradation of stroma components [21, 129, 138, 139]. Moreover, several reports showed their values to induce cancer cell death and the therapeutic potential of these agents as an adjuvant in combination therapies. Furthermore, several studies have illustrated their activities in prostate, breast, colorectal and pancreas cancers, as well as chemopreventive activity against hematopoietic malignancies and lung cancer patients with chronic obstructive pulmonary disease [140, 141]. Furthermore parallel targeting of different dysregulated pathways in GI, such as PI3K/Akt/mTOR, Wnt/b-catenin, TGF- β , RAS/MAP/ERK pathways are required to

overcome cell resistance or suppress the possible feedback loop between these signaling pathways [142]. However we can not exclude the possible side effect of different cytotoxic agents which can thereby enhanced toxicity. These provide a proofs of concept of the need for assessing natural compound, such as curcumin or crocin as well [143][107-108].

Authors Insight On the Topic

The future research should work on the (1) optimization and evaluation of statins alone or their combination with other dysregulated pathways, (2) identification of GI patient who could most benefit from therapy, (3) recognition of markers which can be used for monitoring treatment response; and to (4) explore molecular mechanism behind the antitumor and chemopreventive mechanisms of these agents in the treatment of gastrointestinal cancers.

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Table 1: The impact of statin therapy in patients with gastrointestinal cancer							
Study	Intervention/ treatment		Phase	Start date	End date	Disease type	Key Word
CRC							
Simvastatin in Colorectal Surgery	Simvastatin	Placebo	3	October 14, 2009	2-Dec-13	<u>Colorectal Surgery (StatCol)</u>	NCT00994903
Rosuvastatin in Treating Patients With Stage I or Stage II Colon Cancer That was Removed by Surgery	Rosuvastatin	Placebo	3	11-Nov-09	April 11, 2016	Stage I or Stage II Colon Cancer	NCT01011478
Crossover Evaluation of Effect of Atorvastatin on PK of Irinotecan in CRC Patients Receiving FOLFIRI	Atorvastatin	FOLFIRI	1	24-May-12	27-Feb-14	Advanced adenocarcinoma of the colon or rectum	NCT01605344
Atorvastatin, Oligofructose-Enriched Inulin, or Sulindac in Preventing Cancer in Patients at Increased Risk of Developing Colorectal Neoplasia	Atorvastatin	Oligofructose-enriched inulin/ Sulindac / placeb / Other: laboratory biomarker analysis	2	12-Jun-06	15-Feb-17	Colorectal	NCT00335504
Cetuximab and Simvastatin in Treating Patients With Advanced or Metastatic Colorectal Cancer	Simvastatin	Biological: cetuximab / Other: laboratory biomarker analysis	2	August 27, 2010	12-Aug-13	Advanced or Metastatic Colorectal Cancer	NCT01190462
Simvastatin and Panitumumab in Treating Patients With Advanced or Metastatic Colorectal Cancer	Simvastatin	Panitumumab	2	27-Apr-10	17-Sep-13	Advanced or Metastatic Colorectal Cancer	NCT01110785
Simvastatin + Cetuximab/Irinotecan in K-ras Mutant Colorectal Cancer	Simvastatin	Cetuximab/Iri notecan	2	24-Jan-11	14-Jun-13	Metastatic colorectal	NCT01281761
Trial of XELIRI/FOLFIRI + Simvastatin Followed by Simvastatin Maintenance in Metastatic Colorectal Cancer	Simvastatin	XELIRI/FOLFIRI	3	10-Nov-10	14-Jun-13	Metastatic Colorectal Cancer	NCT01238094
Phase II Study of Simvastatin Plus Irinotecan, Fluorouracil, and Leucovorin (FOLFIRI) for Metastatic CRC	Simvastatin	FOLFIRI	2	12-Apr-06	2-Feb-12	Metastatic CRC	NCT00313859
Rosuvastatin in the Treatment of Rectal Cancer	Rosuvastatin		2	7-Oct-15	June 14, 2018	Rectal Cancer	NCT02569645

A Single Arm, Phase II Study of Simvastatin Plus XELOX and Bevacizumab as First-line Chemotherapy in Metastatic Colorectal Cancer Patients	Simvastatin	capecitabine, oxaliplatin, and bevacizumab	2	3-Jan-14	17-Jan-18	Metastatic Colorectal Cancer Patients	NCT02026583
Capecitabine Plus Simvastatin in Locally Advanced Rectal Cancer Patients	Simvastatin	capecitabine with radiation	2	12-Jun-14	17-Jan-18	Adenocarcinoma of Rectum	NCT02161822

Liver							
Simvastatin in Preventing Liver Cancer in Patients With Liver Cirrhosis	Simvastatin	Placebo / Questionnaire Administration / Other: Laboratory Biomarker Analysis	2	21-Nov-16	17-Jul-18	Cirrhosis	NCT02968810
Effects of Statin on Hepatocellular Carcinoma Recurrence After Liver Transplantation	Statins			April 6, 2018	April 6, 2018	Hepatocellular Carcinoma	NCT03490461
The Combination Effect of Statin Plus Metformin on Relapse-free	Statins	Metformin	2	30-Jun-16	19-Apr-17	Hepatocellular Carcinoma	NCT02819869
Statin for Preventing Hepatocellular Carcinoma Recurrence After Curative Treatment (SHOT)	Atorvastatin	Placebo Oral Tablet	4	19-Jan-17	25-Jan-17	HepatoCellular Carcinoma	NCT03024684
Statin Combination Therapy in Patients Receiving Sorafenib for Advanced Hepatocellular Carcinoma	Atorvastatin	Placebo Oral Tablet	2	7-Sep-17	11-Jan-18	Advanced Hepatocellular Carcinoma	NCT03275376
Pravastatin Intervention to Delay Hepatocellular Carcinoma Recurrence	Pravastatin Pill	Placebo Oral Tablet	2	17-Jul-17	July 18, 2018	Hepatocellular Carcinoma Liver Cirrhoses	NCT03219372
Randomized Trial Sorafenib-Pravastatin Versus Sorafenib Alone for the Palliative Treatment of Child-Pugh A Hepatocellular Carcinoma	Pravastatin	Sorafenib + Pravastatin	3	19-Jul-13	May 13, 2014	Child-Pugh A Hepatocellular Carcinoma	NCT01903694
Sorafenib Tosylate With or Without Pravastatin in Treating Patients With Liver Cancer and Cirrhosis	Pravastatin sodium	Sorafenib Tosylate	3	25-Feb-10	27-May-16	Liver Cancer and Cirrhosis	NCT01075555
Palliative Treatment of Hepatocellular Carcinoma in Patient With CHILD B Cirrhosis (PRODIGE 21)	Pravastatin	sorafenib / Sorafenib + Pravastatin/ Other: patients receiving best supportive care	2	20-May-11	12-Apr-17	Hepatocellular carcinoma CHILD B	NCT01357486
Efficacy and Safety Study of Sorafenib Plus Pravastatin to Treat Advanced Hepatocarcinoma (ESTAHEP-2010)	Pravastatin		2	17-Aug-11	Jun-17	Advanced hepatocarcinoma	NCT01418729
Gastric cancer							
Trial of XP (Capecitabine/CDDP) Simvastatin in Advanced Gastric Cancer Patients	Simvastatin	Placebo (capecitabine-cisplatin (XP))	3	6-Apr-10	17-Feb-17	Gastric cancer	NCT01099085
A Phase I Study of High Dose Simvastatin in Patients With Gastrointestinal Tract Cancer Who Failed to Standard Chemotherapy	Simvastatin		1	January 4, 2018	December 2019	Stomach Cancer	NCT03086291
Role of Statin on the Gastric Inflammation in Patients at High Risk of Gastric Cancer	Simvastatin	Placebo	Not Applicable	19-Mar-13	28-May-14	Early Gastric Cancer or Gastric Adenoma	NCT01813994

Pancreatic Cancer							
Trial of Simvastatin and Gemcitabine in Pancreatic Cancer Patients	Simvastatin	Gemcitabine+ simvastatin / Gemcitabine+ Placebo	2	23-Jul-09	17-Feb-17	Pancreatic Cancer	NCT00944463
Study of the Safety, Tolerability and Efficacy of Metabolic Combination Treatments on Cancer (METRICS)	Atorvastatin	Metformin Doxycycline Mebendazole	3	28-Jul-14	3-Aug-18	CancerOverall Survival	NCT02201381
Esophageal Cancer / Stomach Cancer							
Study to Evaluate the Efficacy of Pravastatin on Survival and Recurrence of Advanced Gastroesophageal Cancer (AGIM-1)	Pravastatin		4	23-Dec-09	27-Jun-11	Esophageal Cancer / Stomach Cancer	NCT01038154
Effect of Simvastatin on Physiological and Biological Outcomes in Patients Undergoing Esophagectomy	Simvastatin	Placebo		2007	2010	Esophagectomy	Shyamsundar, M., et al. (2014)[144]

